

EU Forum

Spreading excellence in allergy and asthma: the GA²LEN (Global Allergy and Asthma European Network) project

**P. Van Cauwenberge¹, J. B. Watelet¹,
T. Van Zele¹, J. Bousquet², P. Burney³,
T. Zuberbier⁴, on behalf of the
GA²LEN partners*¹**

¹Department of Otorhinolaryngology, Ghent University Hospital, Ghent, Belgium; ²University Hospital and INSERM U454, Montpellier, Institut Pasteur Paris, France; ³Department of Public Health Sciences, Guy's, King's and St Thomas' School of Medicine, King's College, London, UK; ⁴Department of Dermatology and Allergy, Charité, Berlin, Germany

*GA²LEN partners are given in Appendix.

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P. Van Cauwenberge, Coordinator GA²LEN
Ghent University Hospital
Department of Otorhinolaryngology
De Pintelaan, 185
B-9000 Gent
Belgium

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Allergic diseases and asthma pose an important and increasing problem for populations and health care systems around the world (1). European research groups have been at the forefront of investigations into the early life influences on the causes of these conditions and management of allergy and asthma (2, 3). Moreover, initiatives from the European Commission have led to a greater collaboration between the European countries and beyond in tackling these problems. It has been shown to be both practical and rewarding to exploit the wide variations in culture, environment and health care systems within Europe to study these issues (4). Collaborative projects such as the European Community Respiratory Health Survey (ECRHS), the International Study of Asthma and Allergy in Childhood (ISAAC), and many other, funded by the European Commission, have clearly demonstrated the ability and advantages of European groups working together (1, 5, 6).

Although allergy and asthma represent a burden in all countries and regions in Europe there is still a lack of permanent structures to support this type of work. The collaboration between European groups so far has often had a relatively narrow methodological focus and has therefore produced only short-term collaborations without a formal enduring structure.

The basic idea of the European Research Area (ERA) is that the aims and goals of future research cannot be met without much greater 'integration' of Europe's research efforts and capacities. The sixth framework programme is a key instrument of ERA with a budget of 17 500 million. For this reason the sixth framework programme introduces new instruments like networks of excellence from which joint strategies can be developed. These networks have clearly defined thematic objectives and will be directed towards advancing scientific and technological knowledge, within medium- to long-term time-frames (7, 8).

Global Allergy and Asthma European Network: Network of Excellence

Global Allergy and Asthma European Network: Network of Excellence (GA²LEN) is the only network of excellence selected by the European Commission, with special interest in Allergy and Asthma. It is a consortium of 24 leading European research teams and two societies (EAACI and EFA) committed to work with each other and to establish a ERA of excellence in the field of allergy and asthma.

The acronym GA²LEN was chosen to commemorate the first respiratory physiologist of Antiquity, Galenus (129–201), who first described the relationship between the nose and the lungs. A grant of 15 million Euros for a period of 5 years will contribute towards linking scientific research centres of excellence throughout Europe under the Sixth Framework Programme for Research.

Structure of GA²LEN

The network consists of 24 centres with high clinical and experimental research competence across Europe conducting and providing platforms for clinical, translational, intradisciplinary and multidisciplinary research.

The other two partners in GA²LEN are the European Academy of Allergology and Clinical Immunology (EAACI), a scientific organization providing training and continuous education in allergy, and the European Federation of Allergy and Airways Diseases Associations (EFA), a patients' organization (see Appendix).

The structure of GA²LEN was designed in a way that fast decisions at every level are possible and transparent, taking into account the inherent complexity of such a large network. Therefore, GA²LEN consists of an assembly, composed of all partners, an executive committee and a management office. An advisory board of 12 representatives from the scientific world, politics and experts in ethical and gender issues, guarantees a long-term commitment from the top management and funding authorities of the participating organizations (Fig. 1).

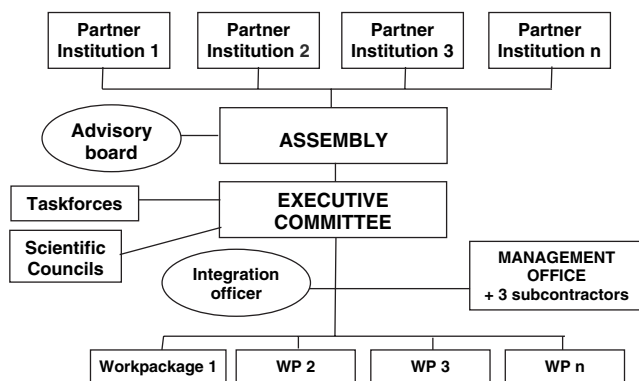


Figure 1. Structure of GA²LEN

Objectives

The objective of GA²LEN is to establish an internationally competitive network of European centres of excellence, to enhance the quality and relevance of research in this area address allergy and asthma in their totality, and, in the long-term, to decrease the burden of allergy and asthma in all regions of Europe. In close collaboration with EFA, GA²LEN will integrate the patient's view into the research programme and disseminate validated scientific information to the patients and policy makers.

Joint programme of activities

The objectives of the GA²LEN NoE can only be reached by a joint programme of activities, including integrating activities, a jointly-executed research programme and activities for the dissemination of knowledge.

Integrating activities. To achieve the integration of research goals the establishment of an open platform for integrating and joint activities is essential. This platform will make it possible to coordinate research using sub-networks, to translate and spread research results, and to provide access to the partners, patients, public, policy makers and industry. These integrating activities are based on several approaches using modern communication systems, common databases, bio-banks, gene banks and bio-informatics. Integrating activities which are specific for GA²LEN, making this a highly competitive network, are the ongoing birth cohorts, epidemiologic studies, a network for clinical trials and the development of a pan-European system of quality management for allergy services.

Jointly-executed research activities. The programmes that are identified for the GA²LEN project that are of major importance to develop new ways of preventing or managing allergies and asthma and will to look at the interaction of genetic and environmental factors, gender and occupational aspects and infection on the development, progression and regression of allergies and asthma. These issues are examined in relation to their influence across the age groups (Fig. 2):

- 1 *Events occurring during intra-uterine life with special focus on the foeto-maternal interface.* Allergic diseases and asthma usually start early in life suggesting that materno-foetal influences are of importance for the development of immunoglobulin E (IgE)-mediated allergic diseases. It is also likely that defects in early development of the lung, as well as the immune system are involved in the pathogenesis of asthma and airway remodelling (9).
- 2 *Early life events in the development of allergic sensitization.* Several environmental factors, including indoor and outdoor pollution, food, life style and infections interact early in life with gene susceptibility

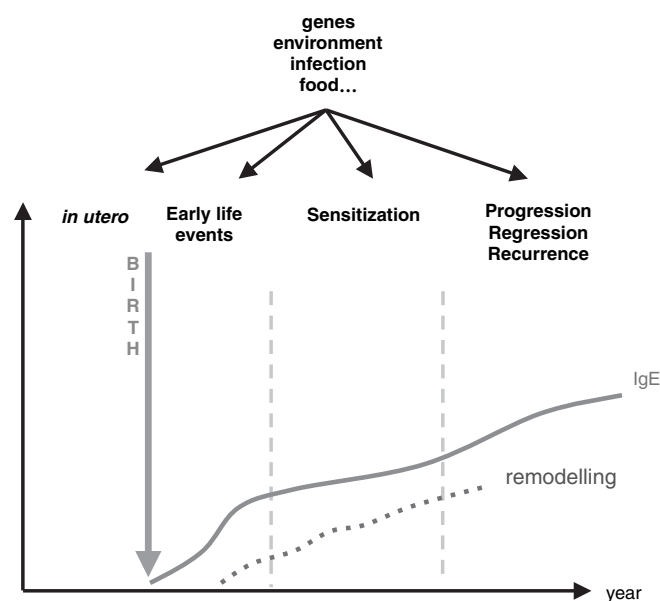


Figure 2. Joint-programme of activities: allergy and interfering parameters through life course

to induce allergenic sensitization. These interactions are probably related to the recent increase in the prevalence of allergy and asthma (10, 11).

- 3 *The translation of allergic sensitization into allergic disease.* Only two-thirds of subjects with allergen specific IgE develop symptoms and a better knowledge of the differences between sensitization and disease is critical to an understanding of the 'allergy march'.
- 4 *The persistence and aggravation of allergic diseases and asthma.* It is also important to understand those factors that determine whether and how allergic diseases persist through childhood into adulthood with a particular interest for tissue remodelling of the upper and lower airways.

There is also a need for new tests and markers to predict the onset of allergy and asthma in early childhood and the persistence and severity of the disease throughout life. The GA²LEN research programme will actively seek for these markers and test them in large clinical trials to assess their value in clinical practice.

The jointly-executed integrated research programme consists of several workpackages (WP) (Fig. 3) that deal with all the issues raised in the above description.

WP 2.1.: Nutrition (WP responsible: University of Southampton, UK). Nutrition, including maternal, infant, childhood and adult diets, is important in the development, persistence and severity of allergic disease including asthma (12). Components of the diet that are of particular interest include the total caloric intake, the exogenous anti-oxidant defences, the lipid content of the diet and dietary electrolytes (13, 14). The European diet

is very diverse and offers an ideal environment to assess the role of diet in the development and maintenance of allergic disease. The objective of the proposed work plan is to develop evidence-based recommendations and policies for prevention and treatment based on a sound and innovative understanding of the role of nutritional factors in the development, duration and severity of allergic diseases.

WP 2.2.1.: Infection: environmental exposure and WP 2.2.2.: Infection: genomics (WP responsible: Ludwig Maximilians Universität München, Germany). European research teams were the first to propose that environmental exposures to microbial substances and parasites confer protection from the development of allergies (15, 16). This effect is consistent over different studies showing reductions in risk of more than 70% associated with exposure. These observations strongly suggest that, by imitating natural powerful tools, the development allergies can be prevented. The GA²LEN partners seek to identify novel immunomodulatory molecules that have therapeutic potential in asthma and allergies. This quest builds on strong epidemiological, immunological and molecular biological evidence for the presence of such microbial-derived compounds in our environment.

WP 2.3.: In and outdoor environment (WP responsible: University of Utrecht, The Netherlands). Exposure to high concentrations of outdoor air pollutants such as fine particles and ozone may exacerbate existing asthma and other allergic conditions, but it is less clear whether pollution affects the incidence of new cases of asthma and allergy (17–19). Experimental studies demonstrate that specific forms of air pollution such as diesel soot act as adjuvants in increasing formation of IgE against common allergens, and in eliciting increased symptoms among already sensitized subjects.

The Network includes centres from many European areas, with different climate and environmental situations. Consequently, there are many aspects of outdoor (and indoor) pollution that can be addressed simultaneously by combining study results, and by performing comparative analyses of existing data. There are already large repositories of house dust samples taken in thousands of European homes in prospective and cross-sectional studies, and advanced methods of microbial assessments including DNA typing will be applied to these samples.

WP 2.4.: Occupation (WP responsible: IMAS Barcelona, Spain). The first main objective of the proposed programme is to examine the effects of occupational exposures in workers employed in nonindustrial indoor environments on the prevalence and incidence of asthma and allergic disease (20, 21). Specific aims include the development and validation of an instrument to assess relevant workplace exposures in nonindustrial indoor environments and to

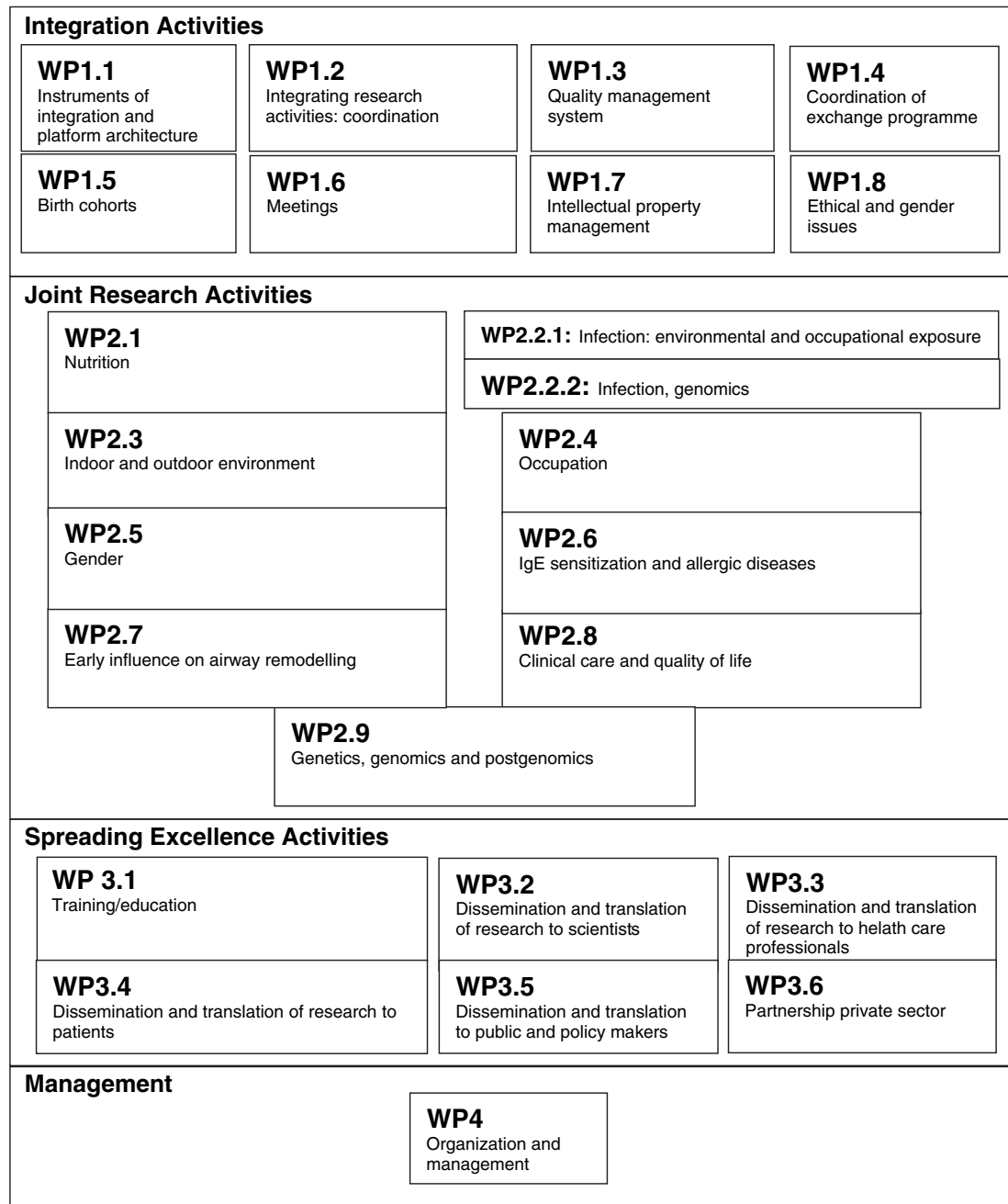


Figure 3. Pert Chart of the WP organization in the GA²LEN network of excellence

assess the associations of these exposures with the prevalence and incidence of asthma and allergic disease among workers.

A second part of the programme will identify the association between cleaning products (in domestic cleaning work) and asthma to evaluate possible effect mechanisms.

WP 2.5.: Gender (WP responsible: INSERM, France). Gender differences in the development, diagnosis and

treatment of asthma and allergy have until now received little attention. Sex differences in lung physiology and immune characteristics are well documented but the role of sex hormones is only hypothesized. This workpackage will focus on three aspects of gender regarding allergic diseases. In the first place consideration will be given to the effects of gender on the management and response to disease. In the subsequent activities recommendations will be developed for integrating gender aspects into medical education to increase

the attention on gender issues in the training of health care professionals and on the implementation of guidelines for gender-based medicine. Secondly gender differences in incidence, prevalence, symptoms and severity of asthma and allergy at different ages and in different populations across Europe will be analysed. Finally analysis of relevant clinical studies and animal models, assessing the influence of sex-hormones, will lead to the development of new protocols regarding sex-specific genetic regulation in allergic diseases.

WP 2.6.: IgE sensitization and allergic diseases (WP responsible: INSERM, France). The synthesis of allergen-specific IgE is required for the development of allergic diseases including asthma, but about one-third of individuals with allergen-specific IgE do not develop symptoms (22). A better understanding of the genetic, molecular and cellular mechanisms underlying the functionality of IgE is of great importance. These include the level of allergen-specific IgE, the affinity of IgE receptor, different IgE epitopes, high levels of allergen-specific IgG₄ which may be protective, a modified Th2 or Treg (T regulatory) response and/or a down-regulation of mast cells and basophils by several mechanisms including FcγRIIB. The comparative analysis of large European studies will make possible to determine the phenotype of asymptomatic subjects with IgE and subjects with respiratory allergies and IgE. Since all tools are available within the network for *Parietaria* pollen allergy there are differences in pollen exposure within NoE centres. This allergenic sensitivity will be used as a model to study the IgE immune response to individual allergens (Par j1, Par j2, and pan-allergens) (23) in subjects who will be mono- and polysensitized with symptoms and without symptoms, and in those who have pan-allergen IgE without exposure. Finally, the comparative analysis of large European birth cohort studies will determine the outcome of the asymptomatic subjects with IgE.

WP 2.7.: Remodelling (WP responsible: CNR Palermo, Italy). Once allergic diseases and asthma have occurred, the major issues are the maintenance, persistence and aggravation of the disease. Although its exact physiologic significance is not completely understood, airway remodelling is associated with asthma severity. Airway remodelling already exists in infants who will subsequently develop asthma, suggesting that pathological defects in asthma occur very early in life and pre-exist to the development of symptoms (24–26). Nasal remodelling exists in rhinitis, but it is far less extensive than in asthma although the same environmental factors are acting in the nose and the bronchi. Differences in nasal and bronchial remodelling may be associated with the interactions of environmental factors on genes of the embryologic differentiation since the nose and the bronchi have a different embryologic origin (ectoderm vs endoderm).

Therefore, DNA microarray testing on genes selected from embryologic differentiation and epithelial mesenchymal trophic unit will be performed on nasal and bronchial samples.

WP 2.8.: Clinical care (WP responsible: Karolinska Institute, Sweden). The very wide variation in allergy practice in Europe indicates either a poor evidence base for best practice, poor implementation of securely based knowledge, or differing priorities and resources. There is a major task to be achieved both in improving the evidence base for best management of patients and for providing tools with which services can be audited and improved within the resource constraints of each country. This workpackage has identified five major gaps in the clinical care of allergic disease. The place of early diagnosis will be studied in relation to the diagnostic tools and biomarkers that are available and used across Europe. The network will allow between-country comparisons of the approach to asthma and allergy patients and direct comparisons of diagnostic procedures and the general adherence to existing international and/or national guidelines. The evidence of primary prevention and early intervention and the evidence for beneficial effects of preventive measures will be reviewed with special attention to the differences in the approach to pharmacological treatment and the need for prescriptions vs over the counter sale.

Also the structure of care and health economy in primary and specialist care will receive attention. Especially the documentation of asthma and allergy treatment in primary care centres (primary care teams). Asthma care in 'primary care asthma teams' should be subjected to controlled clinical trials. The last part of the workpackage will evaluate the needs and quality criteria for the organization of new pan-European clinical trials. This work will result in recommendations regarding outcome measures when monitoring and evaluating clinical asthma and allergy trials. Cross-sectional studies focused on the relationship between asthma status and treatment traditions in different countries will be established and will provide a platform for formation of directed hypotheses concerning the course of the disease. These hypotheses should lead to longitudinal, prospective, studies of the disease comparing pharmacological and nonpharmacological.

WP 2.9.: Genetics (WP responsible: INSERM, France). Several hypotheses regarding interactions between genes and environment are already established and are relevant to the programmes on nutrition, infection and environment.

Replication of associations in different populations is critical for establishing the role of gene variants, as is an understanding of their role, their interaction with (modifiable) environmental factors and their public health importance. This WP aims to build a 'life-span'

test sample for association studies and interaction with environmental (deleterious and protective) factors. Critical periods to be considered are early life, childhood, around puberty, middle age, menopausal period (women), ageing. Furthermore, the WP partners want to build a representative sample for association studies over the life span to assess the public health importance of established deleterious or protective variants by representative samples in various countries. Finally, this WP proposes to develop postgenomic asthma and allergy epidemiology in Europe. Setting up standards for collecting appropriate blood sample collections (including serum, plasma, erythrocytes, DNA and RNA) of high quality in the long-term is crucial. Nanotechnologies and the development of proteomics and metabolomics allow development of a new phase of epidemiological research in conjunction with basic scientists, specifically from the Network and its partners.

Dissemination of excellence. GA²LEN devotes a substantial proportion of its energy and funding towards the training and education of postgraduate scientists (both clinical and nonclinical). The knowledge generated inside the network will be directed to undergraduates and postgraduates by means of education, training and exchange programmes in order to achieve harmonization of the training in allergy and asthma in all regions of Europe. The efforts will essentially be geared at the development and transfer of research competencies, the consolidation and widening of researchers' career prospects, and the promotion of excellence in European research. A substantial amount of the GA²LEN funding will be devoted to GA²LEN exchange grants for clinical and research training.

One of the major objectives of GA²LEN is to assist EU and national policy makers to make recommendations and directives regarding allergy and asthma. Therefore, GA²LEN will help policy makers to form policies and directives, in particular on primary and secondary prevention strategies, school and work policies, and disease management outcomes.

GA²LEN should also help to recognize the importance of the EU involvement in the understanding of allergy and asthma to benefit to patient's health (4, 16, 27–29) by the publication in Allergy (30) of major programmes.

Finally, validated information shall be provided to patients and the public by increasing the awareness of allergy and asthma and by providing evidence-based advice to patients and parents, industry and other stakeholders.

Perspectives and conclusions

GA²LEN aims to strengthen, inside and beyond the network, excellence in allergy and asthma research by consolidating past and future achievements into a formal and enduring structure. This structure forms a unifying link between the research community and the community of patients and policy makers in Europe. GA²LEN wants to harmonize research, training and disease management of allergy and asthma. This network of excellence provides a mechanism for the more rapid completion of new clinical trials, helping industry to improve competitiveness in this area, for the timely implementation of new knowledge into policy and clinical practice throughout Europe. GA²LEN represents Europe's most important attempt to mobilize against the growing burden of allergies and asthma. GA²LEN is a good example of what can be done to challenge a major public health menace.

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Appendix. List of GA²LEN founding partners

Country	Institution	Contact person
Belgium	University of Ghent	Paul Van Cauwenberge
EAACI	European Academy of Allergology and Clinical Immunology	Ulrich Wahn
EFA	European Federation of Allergy and Asthma Associations	Erka Valovirta
Austria	University of Vienna Medical School	Georg Stingl
Denmark	Odense University Hospital	Carsten Bindlev-Jensen
Finland	Helsinki University Central Hospital	Tari Haahtela
France	INSERM	Jean Bousquet
Germany	Charité, Universitätsmedizin-Berlin	Torsten Zuberbier
Germany	Ludwig Maximilians Universität München	Erika von Mutius
Germany	Technische Universität München	Johannes Ring
Greece	National and Kapodistrian University of Athens	Nikos Papadopoulos
Italy	Consiglio Nazionale delle Ricerche (CNR), div. Rome and Palermo	Sergio Bonini and A. Maurizio Vignola†
Italy	University of Genoa	G. Walter Canonica
The Netherlands	Academic Medical Center Amsterdam	Wytske Fokkens
The Netherlands	University of Utrecht	Bert Brunekreef
Norway	Voksensentoppen BKL, National Hospital, Oslo	Carsten Kai-Hakon
Poland	Jagiellonian University Medical College Krakow	Andrzej Szczeklik
Poland	Medical University of Lodz	Marek Kowalski
Portugal	Universidade de Coimbra	Ana Todo Bom
Spain	Institut Municipal Investigacio Medica (IMIM) Barcelona	Josep Anto Boque
Spain	Autonoma University of Madrid	Carlos Lahoz
Sweden	Göteborg University	Jan Lötvall
Sweden	Karolinska Institutet	Sven-Erik Dahlén
Switzerland	Swiss Institute of Allergy and Asthma research (SIAF)	Cezmi Akdis
UK	University of London	Peter Burney
UK	University of Southampton	Anthony J. Frew

†Deceased.